SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

2003M-0569

SS1

SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name: Ceramic/Ceramic Hip

Device Trade Name: Keramos™ Ceramic/Ceramic Total Hip System

Applicant's Name and Address:

Encore Medical, L.P.
9800 Metric Blvd.
Austin, TX 78758

Product Development Protocol (PDP) Number: D980003

Date of Panel Meeting: April 27, 1998

Date of FDA Approval of PDP: July 21, 1998

Date of FDA Approval of Notice of Completion: November 26, 2003

II. Indications For Use

The Keramos™ Ceramic/Ceramic Total Hip System is indicated for use in patients requiring primary total hip arthroplasty for the treatment of inflammatory tissue disorders and non-inflammatory degenerative joint disease, including osteoarthritis, post-traumatic arthritis or secondary arthritis, and avascular necrosis.

III. Contraindications

- Infection
- Sepsis
- Osteomyelitis
- Rapid joint destruction or bone adsorption apparent on roentgenogram
- Skeletally immature patients and cases where there is a loss of abductor musculature, poor bone stock, or poor skin coverage around hip joint which would make the procedure unjustifiable
- Uncooperative patient, or a patient with neurologic disorders and incapable of following instructions
- Osteoporosis
- Metabolic disorders which may impair bone formation
- Osteomalacia
- Distant foci of infections (which may cause hematogenous spread to the implant site)
- Obesity

- Foreign body sensitivity

IV. Warnings and Precautions

The warnings and precautions can be found in the Keramos physicians labeling.

V. Device Description

The Keramos™ Ceramic/Ceramic Total Hip System is a ceramic-on-ceramic hip system. It consists of alumina ceramic bearing surfaces, i.e., femoral head and acetabular insert (or liner) combined with a compatible metal acetabular shell. The system is provided sterile via gamma irradiation (minimum 25 kGy). For the purposes of this study the acetabular shell and bearings were implanted in combination with one of three commercially available Encore femoral stems. The use of commercially available Encore Bone Screws was optional.

Acetabular Shell

The metal shell is fabricated from wrought titanium alloy (Ti-6Al-4V) that conforms to ASTM F136. The outside surface of the shell is coated with commercially pure titanium beads (ASTM F67) for the purpose of providing a porous surface for enhanced press-fit (cementless) fixation. The hemispherical shell is available in outer diameter sizes ranging from 48 mm to 66 mm. The outside of the shell flares outward 1 mm approximately 5 mm below the equator. This results in the face of the shell being 2 mm greater in diameter than the spherical diameter of the shell. The inside of the shell is conical with a series of three angled flats at the dome. The conical feature serves to provide a secure Morse type taper lock to attach the insert to the shell. A threaded hole is located at the dome of the shell to accept an instrument used for positioning and inserting the acetabular shell. Additional screw holes within the dome of the shell are provided to allow for supplemental fixation with cancellous bone screws, if desired.

Acetabular Insert

The acetabular insert, or liner, is manufactured from alumina ceramic, Al_2O_3 (ISO 6474). The outside geometry is conical with two angled surfaces leading to a flat dome. The conical geometry mates with the corresponding geometry in the shell to form the insert/shell attachment mechanism. The alumina insert is available in two internal diameters: 28 mm and 32 mm. The 28 mm insert may be used with acetabular shells with outer diameters ranging from 48 mm to 66 mm, and the 32 mm insert is for use with acetabular shells with outer diameters of 52 to 66 mm.

Femoral Heads

The femoral heads are fabricated from alumina ceramic (ISO 6474) which is the same material used for the acetabular insert. The heads are available in 28 mm and 32 mm diameters and three neck lengths. These femoral heads have been previously cleared for use with polyethylene acetabular inserts in K955563.

Femoral Stems

The stems used in this study are from Encore's Foundation (K973302), Revelation (K973685), and Linear (K974294) Hip Systems. They are porous-coated and intended for press-fit (cementless) fixation. These porous-coated femoral stems are made from wrought Ti-6Al-4V (ASTM F136) with a porous coating of commercially pure titanium beads (ASTM F67, grade 2). The Foundation stem is available with and without a calcar collar. The Revelation is a collarless design with a neck in 12° of anteversion. The stem/neck angle is 130°. The Linear stem is collarless and available with a standard offset and a lateralized offset that provides additional lateralization without increasing leg length. The stem/neck angle is 135°. These three hip stems provide surgeons with a wide array of choices to address differing patient anatomies and needs.

VI. Alternative Practices and Procedures

Alternative procedures include the election not to have surgery and use a more conservative treatment consisting of reduced activity and pain medication, or the decision to have surgery with another commercially available total hip prosthesis. Currently, the most commonly used implant materials for total hip arthroplasty include metallic prostheses using articulating bearing surfaces made of a combination of metallic and ultra-high molecular weight polyethylene (UHMWPe). Other hip prostheses use ceramic/UHMWPe, metal/metal, or ceramic/ceramic bearing articulations. Total hip prostheses are implanted by either cemented or uncemented techniques.

VII. Marketing History

The Keramos™ Ceramic/Ceramic Total Hip System has not been marketed in the United States or any foreign country.

VIII. Potential Adverse Effects of the Device on Health

Clinical testing was performed to determine if the Encore Keramos™ Ceramic/Ceramic Total Hip System was as safe and effective as the marketed control device (ceramic/polyethylene).

Patients were randomized into 1 of 2 treatment groups: investigational ceramic/ceramic device or control ceramic/polyethylene device. The investigational group consisted of 237 patients (250 implants) and the control group consisted of 242 patients (250 implants).

Patients were followed until the last patient implanted attained their 2-year evaluation. An additional 400 patients (447 hip implants) were implanted with the investigational device by study investigators under 'continued access' provisions.

Table 1, below, includes a time course distribution of the operative site adverse events reported for this study. The table includes all operative site events reported through two years follow-up for the investigational and control patients enrolled in the original study, as well as the continued access patients implanted with the investigational device.

Table 1. Time Course Distribution of Operative Site Adverse Events for Ceramic/Ceramic Total Hip System vs. Control Ceramic/Polyethylene Hip System Out to 24 Months Post-Operatively.

Operative Site Adverse Events	Ceramic/Ceramic Original Study Population 250 cases (237 patients) enrolled						Continued Access Population 447 cases (400 patients) enrolled						Ceramic/Polyethylene Control Population 250 cases (242 patients) enrolled					
Visit	Op	6	12	24	Tot	%	Op	6	12	24	Tot	%	Op	6	12	24	Tot	%
N = cases evaluated	250	220	207	196	-	-	447	343	272	115	-	-	250	216	205	187	-	-
Revision*	0	1	0	0	1	.4%	0	1	0	1	2	.4%	0	5	0	1	6	2 4%
Fractured Liner	1	0	0	0	1	4%	0	0	0	0	0	0%	0	0	0	0	0	0%
Clicking w/Walking	0	0	0	1	1	4%	0	0	0	0	0	0%	0	0	0	0	0	0%
Hip Pain	2	2	1	1	6	2 4%	0	1	0	0	1	2%	0	0	0	3	3	1 2%
Dislocation	7	0	0	0	7	2 8%	6	2	0	1	9	2%	10	0	0	0	10	4%
Fracture Femur	8	0	0	0	8	3 2%	6	0	0	0	6	1 3%	2	0	0	0	2	8%
Trochanteric Bursitis	2	1	0	2	5	2%	0	3	1	1	5	1 1%	2	1	5	2	10	4%
Wound Infection	2	0	2	1	5	2%	1	1	0	0	2	.4%	2	0	2	0	4	1 6%
DVT	3	1	0	0	4	1.6%	1	0	0	0	1	.2%	4	0	0	0	4	1 6%
Hematoma	2	0	1	0	3	1 2%	2	0	0	0	2	4%	1	0	0	0	1	.4%
Flexor Tendonitis	0	1	0	0	1	4%	0	1	0	0	1	2%	0	0	0	0	0	0%
Acetabular Cell Tumor	1	0	0	0	1	.4%	0	0	0	0	0	0%	0	0	0	0	0	0%
Heterotopic Ossification	0	1	0	0	1	.4%	0	1	1	0	2	4%	0	3	0	0	3	1 2%
Trochanteric Wire Break	1	0	0	0	1	.4%	4	0	0	0	4	.9%	1	0	0	0	3	1 2%
Acetabular Lossening	0	0	0	0	0	0%	0	0	0	0	0	0%	1	0	0	1	2	.8%
Leg Length Inequality	0	0	0	0	0	0%	0	0	0	0	0	0%	2	0	0	0	2	.8%
Fracture Pubic Rami	0	0	0	0	0	0%	0	0	0	0	0	0%	0	0	1	0	1	4%
Abductor Weakness	0	0	0	0	0	0%	0	0	0	0	0	0%	1	0	0	0	1	.4%
Misoriented Shell	0	0	0	0	0	0%	1	0	0	0	1	2%	0	0	0	0	0	0%
Hip Infection	0	0	0	0	0	0%	2	0	1	0	3	67%	0	0	0	0	0	0%
TOTAL	29	7	4	5	45		23	10	3	3	39		28	9	8	7	52	

Op = intraoperatively, 6 = 6 months, 12 =12 months, 24 = 24 months postoperative, Tot = total Table includes all operative site adverse events - device related *and* 'unrelated' % = total number of a particular adverse event reported divided by number of *cases enrolled* * Revisions, included here, were not included among the operative site adverse events reported and analyzed by the sponsor However, the adverse events that *led* to the revisions *were* reported and analyzed The sponsor listed and analyzed revisions separately under survivorship

The following risks and complications may be reported for *any* total hip replacement surgery. These include, but are not limited to: death, cardiovascular disorders like pulmonary embolism, myocardial infarction, or deep vein thrombosis (DVT), infection, nerve impingement or damage, heterotopic bone formation, material sensitivity reactions, gastrointestinal complications, genitourinary complications, fractures of the femur, migration of the prosthesis, loosening of total hip components, decreased range of motion, shortening or lengthening of the extremity, aggravated conditions in other joints or back due to intraoperative trauma, leg length discrepancy, or muscular deficiencies, localized progressive bone resorption (osteolysis), excessive wear from damage to mating wear surfaces or debris particles, pain, subluxation, dislocation, and revision of the hip prosthesis.

While the expected life of total hip replacement components is difficult to estimate, it is finite. Component wear, breakage of the femoral head or acetabular insert, and component dissociation are potential adverse effects related to ceramic/ceramic hip prostheses.

IX. Summary of Studies and Results

A. Preclinical Testing

Preclinical testing and literature analyses were performed addressing the issues of the alumina ceramic insert/metal shell attachment, component fracture, compression testing, and wear. All insert testing was performed on the 28 mm inner diameter ceramic insert with the thinnest wall. This is the weakest component.

1. **Biocompatibility**

Acceptance Criteria: This material must be as biocompatible as UHMWPe, cobalt-chromium-molybdenum (CoCrMo) alloy, and titanium alloy (Ti-6Al-4V).

Numerous studies (cited in the PDP) have looked at tissue response of alumina particles in both animals and humans. All have shown that few granulocytes or lymphocytes are associated with alumina, contrary to that seen with metals. Results indicate that compared to UHMWPe, CoCrMo, and Ti-6Al-4V, the tissue reaction is lowest for alumina, followed by CoCrMo, Ti-6Al-4V, and UHMWPe. In addition, no fibrosis was induced by alumina, unlike with polymers and metals.

In one referenced study the human body's response to alumina particles was evaluated by examining the joint capsule tissues of revised ceramic/ceramic total hips. The review of these examinations, and comparison to those reported by others, led to the conclusion that the overall foreign-body reaction to ceramic particles is less intense than the reaction towards other wear debris.

Although no biocompatibility testing was specifically performed on the device couple to be marketed by Encore, these acceptance criteria were agreed to prior to approval of the PDP, and this exact same method of analysis (and test data) was included in the PDP at the time of its approval.

Biocompatibility of bulk alumina was not addressed because femoral heads manufactured from this material are currently cleared for commercial distribution and have been on the market for over 15 years. In addition, the Master Files (MAF) from CeramTec contain extensive biocompatibility information on bulk and powdered alumina. The acceptance criteria were met as specified.

2. **Wear**

Acceptance Criteria: The volume of wear particles or amount of linear wear can be no greater for ceramic/ceramic than for metal/polyethylene.

Various literature sources were cited that included both in-vivo and in-vitro data which suggests that (alumina) ceramic/ceramic wear is

significantly less than metal/poly wear. The following wear rates of articulating surfaces were reported:

Table 2. Reported Wear Rates for Various Bearing Couples

Wear Rate	Author	In-vivo/In-vitro
Metal/Poly		
.075-.150mm/yr	Callaghan, et al 1995	In-vivo
.2mm/yr	Zichner and Willert 1992	In-vivo
.08-.2mm/yr	Clarke 1991	Both
.2mm/yr	Dörre 1992	In vitro
Ceramic/Ceramic		
.001mm/10^6 cycles*	Walter 1996	In vitro
.000025mm/yr	Dorlot et al 1989	In-vivo
.002mm/yr	Dörre 1992	In vitro

*10^6 cycles equates to 1 year of walking

The ceramic/ceramic had wear rates ranging from 37 to 8000 times less than metal/polyethylene. Although no wear testing was performed on the specific device couple to be marketed by Encore, these acceptance criteria (along with this method of analysis and test data) were provided in the PDP and agreed to (by FDA) prior to its approval. The acceptance criteria were met as specified.

3. **Insert/Shell Attachment**

Acceptance Criteria: The attachment of the ceramic insert to the shell should be sufficient to withstand the loads seen in-vivo with a safety factor of five.

The physiologic loads the insert/shell interface is exposed to are shear loads caused by frictional resistance between the head and insert. Under worst case conditions it was demonstrated, from the literature, that the frictional resistance between the ceramic head and insert when subjected to a 3 kN axial load was 5 Nm under dry conditions and 0.5 Nm when tested in Ringer's solution.

Therefore, the insert rotational stability and resistance to lever out needed to exceed 25 Nm in the dry state and 2.5 Nm in the wet state.

Testing was performed to confirm that the ceramic insert/shell attachment strength met this criterion. After assembling the insert/shell with a 2 kN axial load it was then tested for torsional resistance. A torsional load was applied until failure occurred. The results showed that this interface would withstand 99.8 Nm (± 43.3 Nm), which is well in excess of the required acceptance criteria (25 Nm). Lever out did not occur at a maximum torque of 95 Nm, again far in excess of the acceptance criteria.

These acceptance criteria (along with this method of analysis and test data) were provided in the PDP and agreed to (by FDA) prior to its approval. The acceptance criteria were met as specified.

4. **Acetabular Component Fracture**

Only the ceramic acetabular insert was considered in this test. Previous testing of the ceramic heads and ceramic head/insert couple were included by reference and in the Compression Testing section, below.

Acceptance Criteria: An FDA guidance document outlines acceptable static and cyclic fracture loads for ceramic heads. This document was also used to establish the acceptable fracture loads for ceramic inserts, i.e. minimum average static fracture load of 46 kN (minimum single fracture load of 20 kN) and minimum fatigue strength of 14 kN at 10 million cycles.

Testing was performed to determine the maximum static and fatigue compression loads to failure on the ceramic insert. Five inserts were tested with a CoCrMo femoral head in axial compression and the average static load to fracture was 63,660 N. Three samples were tested in a fatigue mode with loads cycling from 1400 N to 14,000 N for 10 million cycles with no sign of cracks or fractures. These pieces were then subjected to static compressive loading and exhibited an average fracture load of 60,400 N. The fracture loads exceeded the FDA requirement and therefore met the established acceptance criteria. These acceptance criteria (along with this method of analysis and test data) were provided in the PDP and agreed to (by FDA) prior to its approval.

5. **Compression Testing**

Acceptance criteria: Acceptance criteria for static loading of the ceramic inserts with ceramic femoral heads was an average failure load of 63.7 kN ± 10%, the failure load of ceramic inserts axially loaded with CoCrMo heads.

A finite element analysis (FEA) of the head/insert assembly was conducted to determine the implant size and orientation that produced the least load to failure in compression loading. Analysis was performed with the insert at 5° intervals of the angles of inclination and rotation. The worst case loading being the loading that produced the highest stress profiles in the analysis. A safety factor of 10 times the worst case loading/stress was established to compare to the material properties of the alumina to be sure it complied with the requirements. Physical testing was performed using the worst case orientation as the actual test orientation. The protocol stated, "A long neck alumina ceramic head attached to a metal taper will load the insert/shell in compression until failure of one of the components."

Five 28 mm ceramic heads and 5 48/50 ceramic inserts were static tested at 60° orientation, based on the results of the FEA. All 5 heads fractured at loads averaging 47.92 kN (10,774 lbs). No inserts fractured. Although the acceptance criteria were not technically met (i.e., 63.7 kN ± 10%), the results demonstrate that the acetabular inserts can withstand greater loads than the femoral heads, and the femoral heads demonstrate that they can withstand loads above the FDA requirement for static axial compression testing (46 kN), even in a more severe loading configuration. Therefore, the ceramic inserts and indeed the entire head/insert/shell assembly appear to be more than strong enough for their intended use. Clinical results to date also support this conclusion as there have been no reports of post-operative fracture of the components. Therefore, it was concluded that the acceptance criteria were met.

B. Clinical Testing

Clinical testing was performed to determine if the Encore Keramos™ Ceramic/Ceramic Total Hip System was as safe and effective as the marketed control device (ceramic/polyethylene). A total of 458 patients (with 500 hip implants) were randomized into 1 of 2 treatment groups: investigational ceramic/ceramic device or control ceramic/polyethylene device. Patients were followed until the last patient implanted attained their 2-year evaluation. Upon completion of enrollment for the study, an additional 400 patients (447 hip implants) were implanted with the investigational device by study investigators through June 30, 2003, under 'continued access' provisions. A total of 17 investigators participated in this study.

The original 500 cases included 250 investigational devices (237 patients) and 250 control devices (242 patients). There were 42 bilateral patients (13 received both investigational devices, 8 received both control devices, and 21 received one of each). These 21 were therefore included in each group (i.e., 13 + 21 = 34 bilateral patients in the investigational group; 8 + 21 = 29 bilateral patients in the control group). This accounts for the discrepancy of 21 between the total number of patients implanted (458) and the combined number of patients enrolled in each treatment group (237 investigational + 242 control = 479), as presented in Table 1. There were a total of 203 unilateral investigational patients and 213 unilateral control patients enrolled into the study (i.e., 416 total unilateral cases enrolled). There were a total of 84 bilateral cases enrolled (47 investigational ([13 x 2] + 21), 37 control ([8 x 2] + 21)).

The sponsor's Notice of Completion (NOC) contains data from 444 of 484 (92%) original implant cases that were at least 2 years past surgery. For any patient not seen at their 2 year visit, the result from their next annual visit was used in the analysis. This provided the 92% follow-up rate on all cases enrolled that were not excluded due to death (9) or revision (7). Nine deaths were reported (6 investigational, 3 control) prior to the 2 year evaluation, and none were study

related. A total of 7 revisions were reported prior to the 2 year evaluation (1 investigational, 6 control).

Table 3, below, provides an accounting of the follow-up numbers on which the safety and efficacy of the subject device system was based.

Table 3. Device Accountability

	Ceramic/Ceramic Original Study Population (n=250)			Continued Access Population (n=447)			Ceramic/PE Control Population (n=250)		
	6 mo	1 yr	≥2 yrs*	6 mo	1 yr	≥ 2 yrs*	6 mo	1 yr	≥ 2 yrs*
Theoretical Follow-up	250	250	**250**	386	317	129	250	250	**250**
^Deaths	0	1	**6**	3	1	1	0	1	**3**
^Revisions	1	0	**1**	0	0	2	5	0	**6**
Expected Follow-up	249	248	**243**	383	316	126	245	244	**241**
Lost To Follow-Up	0	0	**14**	0	0	3	0	0	**26**
Actual Follow-Up %	88.3% 200/249	83.5% 207/248	**94.2% 229/243**	89.6% 343/383	86% 272/316	91.3% 115/126	87.8% 216/246	84% 205/244	**89.2% 215/241**

Theoretical Follow-Up (TFU) = theoretical number of cases available for follow-up; Expected Follow-Up (EFU) = TFU minus deaths and revisions; Actual Follow-Up (AFU) = cases that had clinical data available at specified follow-up interval; Lost to Follow-Up (LTFU) = EFU minus AFU; AFU (%) = AFU / EFU; * includes 2 year or next available evaluation (3 or 4 year); n = number of cases; ^ cumulative from previous follow-up interval; table includes bilateral cases and protocol deviations

Of the 444 cases with at least 2 year data available, there were 361 unilateral cases available for the effectiveness evaluation; 423 *patients* (out of 463 patients enrolled into both groups and not excluded due to death (9) or revision (7)) for the systemic safety evaluation; and, 444 available *cases* for the operative site safety evaluation.

There were 343 osteoarthritis (160 investigational, 183 control), 85 avascular necrosis (51 investigational, 34 control), 16 post-traumatic (9 investigational, 7 control), 9 secondary arthritis (6 investigational, 3 control), 19 inflammatory (8 investigational, 11 control), 7 Fx/dislocation (4 investigational, 3 control), and 21 'other' (12 investigational, 9 control) cases enrolled into this study.

1. **Inclusion and Exclusion Criteria for the PDP Study**

Inclusion Criteria

Patients meeting all of the following inclusion criteria were enrolled into the study:

- Diagnosed with inflammatory tissue disorders (e.g. rheumatoid arthritis, lupus, etc), osteoarthritis, post-traumatic arthritis or secondary arthritis, or avascular necrosis,
- Less than 70 on preoperative Harris Hip Score (HHS), --
- Required a primary total hip replacement, and
- Patient was likely to be available for evaluation for the duration of the study.

Exclusion Criteria

Patients who met one of the exclusion criteria were not eligible for enrollment in the study:

- Physical conditions that would eliminate adequate implant support or prevent the use of an appropriately sized implant (e.g., tumor),
- Previous surgery that has adversely affected bone stock (such as some hip pinning or some osteotomies),
- Prior total hip replacement,
- Insufficient quality or quantity of bone resulting from conditions such as: Cancer, where radiation has destroyed the available bonestock, Congenital dislocation, Metabolic bone disease of the upper femur or pelvis, Femoral osteotomy revision, Girdlestone revision, Active infection of the hip joint, Old or remote infection, Other conditions that lead to inadequate skeletal fixation,
- Neurological conditions that might hinder patient's ability to follow study procedures, e.g., to restrict physical activities (e.g., Severe Parkinson's, CVA on affected side),
- Patient's mental condition that may interfere with his ability to give an informed consent or willingness to fulfill the required follow-up of the study such as: Mental illness, Senility, Drug Abuse, Alcoholism,
- Conditions that place excessive demands on the implant: Charcot's joints, Muscle deficiencies, Multiple joint disabilities, Refusal to modify postoperative physical activities, Skeletal immaturity, Obesity (50% over recorded body weight mass index), and
- Greater than or equal to 70 on preoperative HHS.

2. Study Population/Demographics

Table 4. Demographics

*Demographics						
Category	Female		Male		Total	
	Study	Control	Study	Control	Study	Control
Number of Cases	112	133	138	117	250	250
Mean Age	55.8	61.9	54.3	59.8	55.0	60.9
Age Range	17-91	19-86	18-87	27-94	17-91	19-94
Mean Preop HHS	42.9	42.7	46.4	46.5	44.8	44.5
HHS Range	8-65	10-68	12-69	12.69	8-69	10-69
Right Hip	53	77	67	58	120	135
Left Hip	59	56	71	59	130	115

*includes bilateral cases; Study = Ceramic/Ceramic; Control = Ceramic/Polyethylene

3. Study Period

The first device in the original study cohort was implanted January 29, 1998, and the last device was implanted January 24, 2001. With 2 year follow-up required on all patients the total duration of this study was 5 years.

4. **Safety and Effectiveness Data**

Study success was based on the safety and effectiveness results obtained at the 2 year (or greater) evaluation. Effectiveness was based on unilateral patients/cases only, whereas safety also included bilateral patients/cases.

Effectiveness of the investigational device as compared to the control device was assessed using the HHS. The compilation and analysis of this data, exhibiting the relief of pain and return to normal function, was collected during the course of this prospective, randomized, controlled clinical trial. The effectiveness analysis was based on unilateral patients only.

Safety was established through comparison of complication rates (device related and unrelated), survival of the implants, and radiographic analyses. Safety analysis included both unilateral and bilateral patients.

Predetermined acceptance criteria were established for each endpoint. The two treatment groups: investigational (ceramic inserts) and control (polyethylene inserts) were compared based on the acceptance criteria that the ceramic/ceramic hip system would perform within 5 points or 5 percentage points for each endpoint (except for complication rates, which used 6 percentage points as the acceptance criteria). The following clinical results of this study show that the Keramos™ Ceramic/Ceramic Total Hip System met these acceptance criteria.

Table 5. Safety and Effectiveness Data

5 Primary Endpoints	Investigational Group	Control Group	Acceptance Criteria
Mean HHS Scores*	92.36	92.16	Met
% of Patients with Related Complications	6.4 %	4.8 %	Met
% of Patients with Unrelated Complications	9.2 %	14.1 %	Met
Device Survival**	99.6 %	97.6 %	Met
Radiographic Failures#	0	0	Met

Does not include continued access data, only data from the original study population; * Includes unilateral patients only (i.e. 186 study and 183 control), all other categories include bilateral patients/devices; ** lack of revision or removal; #lack of specified radiolucencies and migration

All scores and percentages reflect the outcome at the 2-year evaluation or if a particular patient missed their 2-year evaluation, the next annual evaluation was used.

Effectiveness

The acceptance criteria for the study effectiveness endpoint of mean HHS, as specified in the PDP protocol, required that the mean HHS for the investigational group be within 5 points of the control group. The total mean HHS scores for the investigational and control groups (92.36 versus 92.16, respectively) differed by 0.2 points, but they were not significantly

different (p=0.7450). While site effect was significant (p<0.0001), treatment-by-site interaction was not significant (p=0.2598). Based on the results presented in the NOC (and amendments), this acceptance criteria has been met.

Safety

The investigational group had a total of 130 reported complications (44 operative site, 86 systemic). This includes all available follow-up visits (i.e. up to 4 years for some patients). The control group had a total of 117 reported complications (48 operative site, 69 systemic). This also includes all available follow-up visits (i.e. up to 4 years for some patients). These numbers include multiple complications occurring in the same patient.

For the investigational group the most commonly identified operative site complications were femoral fracture (8), dislocation (7), hip pain (6), trochanteric bursitis (5), wound infection (5), deep vein thrombosis (4), and hematoma (3). The most commonly identified systemic complications were contralateral hip pain (23), knee pain (18), spinal problems (14), and cancer (4).

For the control group the most commonly identified operative site complications were dislocation (10), trochanteric bursitis (10), revision (6), wound infection (4), deep vein thrombosis (4), hip pain (3), heterotopic ossification (3), and trochanteric wire break (3). The most commonly identified systemic complications were contralateral hip pain (21), spinal problems (12), knee pain (10), and foot problems (3).

See Table 1, Section VIII, for a time course distribution of all operative site adverse events reported through the two year visit, including those reported for continued access patients.

The acceptance criteria for the study safety endpoint of complications, as specified in the PDP protocol, required that the device related and unrelated complication rates for the investigational group be within 6 percentage points of the control group. The device related complication rates (% of patients with device related complications) reported for the investigational and control groups (i.e., 6.4% versus 4.8%, respectively) differed by 1.6%, with the investigational group achieving a slightly higher complication rate, but they were not significantly different (p=0.5224). The unrelated complication rates for the investigational and control groups (9.2% versus 14.1%, respectively) differed by 4.9%, with the control group achieving the higher complication rate. These two groups were not significantly different (p=0.1094). Based on the results presented in the NOC (and amendments), this acceptance criteria has been met.

The acceptance criteria for the study safety endpoint of survivorship, as specified in the PDP protocol, required that the survivorship rate for the investigational group be within 5 percentage points of the control group. The total survivorship rates for the investigational and control groups (99.6% versus 97.6%, respectively) differed by 2%. The differences were not significant. One investigational device (dislocation) and 6 control devices were revised through the 2 year follow-up endpoint. Based on the results presented in the NOC (and amendments), this acceptance criteria has been met.

The acceptance criteria for the study safety endpoint of radiographic failure, as specified in the PDP protocol, required that the failure rate for the investigational group be within 5 percentage points of the control group. There was no difference in radiographic failure rates since neither group reported any radiographic failures. Based on the results presented in the NOC (and amendments), this acceptance criteria has been met.

Continued Access Patients

After enrollment of the initial study cohort, investigators were allowed to continue implanting under 'continued access'. During this phase, 400 patients received 447 investigational devices through June 30, 2003. These numbers reflect 47 bilateral patients. Another 16 patients (included in the 400) received a device in this phase and had previously received a hip replacement as part of the original cohort.

A total of 272 out of 317 patients (86%) appeared for their 1 year visit. Average HHS was 90.6. For the 115 of 129 patients (91%) who appeared for their 2 year visit the average HHS was 91.4. There have been no radiographic failures, osteolytic lesions, or device migration reported. A total of 70 complications have been reported in 59 patients. This includes 33 systemic and 37 at the operative site.

For the continued access group the most commonly identified operative site complications were dislocation (9), femoral fracture (6), trochanteric bursitis (5), trochanteric wire break (4), hip infection (3), hematoma (2), heterotopic ossification (2), and wound infection (2). The most commonly identified systemic complications were contralateral hip pain (9), back pain (8), knee pain (6), and unrelated death (5). In addition, two hips from this group have been revised (and are included in Table 1). One for an infection in the hip at 8 months post-operative, and one for dislocation at 2 years post-operative.

5. **Patient Complaints**

There have been no patient complaints not previously reported under adverse experiences.

6. **Device Failures and Replacements**

At two years follow-up there was one patient in the investigational treatment group revised for recurrent dislocations. There were six control patients revised during this same evaluation period.

Two investigational patients were revised after their three year follow-up. Both of these patients were deemed failures at their 2 year evaluation due to HHS scores of less than 80.

7. **Patient Accountability**

Accountability based on patient's status at the ≥2-year evaluation is provided in Table 3.

8. **Statistical Analyses**

Potential bias was evaluated in the statistical analyses by testing for treatment-by-site interactions. Continuous variables (age, preoperative HHS, and two-year HHS) were tested using a two-way ANOVA that included terms for treatment, site, and treatment-by-site interaction. Categorical variables (sex, related and unrelated post-operative complications, survivorship, and proportion of patients with two-year HHS scores less than 80) were tested using the CMH test adjusting for site. Treatment-by-site interactions were tested using the Breslow Day test for homogeneity of the odds ratio.

Mean two-year post-operative HHS was presented by site and for all sites combined (total). The total mean scores for the study and control groups (92.36 versus 92.16, respectively) differed by 0.2 points with the investigational group achieving a slightly higher mean score, but they were not significantly different ($p=0.7450$). While site effect was significant ($p<0.0001$), treatment-by-site interaction was not significant ($p=0.2598$).

The percentage of patients with related complications was presented by site and for all sites combined (total). The total complication rates for the study and control groups (6.4% versus 4.8%, respectively) differed by 1.6% and were not significantly different ($p=0.5224$). The percentage of patients with unrelated complications was presented by site and for all sites combined (total). The total unrelated complication rates for the study and control groups (9.2% versus 14.1%) differed by 4.9%, with the control group showing the higher complication rate. These two groups were not significantly different ($p=0.1094$).

Results for survivorship were presented by site and for all sites combined (total). The total survivorship rates for the study and control groups (99.6% versus 97.6%, respectively) differed by 2%. Furthermore, the differences were not significant and the study survivorship rate was higher than the control.

X. Conclusions Drawn From Studies

A. Discussion of Valid Scientific Evidence

Pre-clinical testing (wear, insert/shell attachment, component fracture, and compression testing) was performed on the ceramic/ceramic hip system Predetermined acceptance criteria were established for each test mode. Test results showed the ceramic/ceramic hip system met the established criteria.

Clinical testing was performed on 500 devices (479 patients) to determine if the ceramic/ceramic device was as safe and effective as the control device. Safety and efficacy were evaluated in relation to HHS scores, complication rates, survival of the devices, and radiographic analyses. Predetermined acceptance criteria were established for each endpoint. The clinical results of this study showed the ceramic/ceramic hip system met the established criteria.

B. Discussion of Data on Safety and Effectiveness

Safety and Effectiveness were assessed using the Harris Hip Scores, complication rates (device related and unrelated), survival of the implants, and radiographic analyses. The two treatment groups: study (ceramic inserts) and control (polyethylene inserts) were compared based on the acceptance criteria that the ceramic/ceramic hip system would perform within 5 points or 5 percentage points for each endpoint (except for complication rates, which used 6 percentage points as the acceptance criteria). The Encore Keramos Ceramic/Ceramic Total Hip System met the established acceptance criteria for all five study endpoints. See Table 5 for details. Therefore, it has been demonstrated that this device system is safe and effective when used as indicated.

C. Risk/Benefit Analysis

Other than the risks generally associated with total hip arthroplasty the following additional risks were identified for the Encore Keramos™ Ceramic/Ceramic Total Hip System: breakage of the ceramic insert or femoral head, the necessity for removal of all ceramic components if one must be removed/revised, and intraoperative chipping of the ceramic insert. Based on the results of this study comparing the study and control treatment groups, there were no increased risks associated with the ceramic/ceramic bearing couple. Safety was assessed based on rates of complications. The study showed both treatment groups to be equivalent. A long-term analysis will have to be performed on the ceramic/ceramic couple to determine any benefits.

XI. Panel Recommendations

At a meeting of the Orthopedics and Rehabilitation Devices Advisory Panel (the Panel), held on April 27, 1998, the Panel recommended, by a vote of 8 to 1, that the subject PDP be found approvable with conditions. These conditions included the following suggested preclinical and clinical protocol changes:

A. Preclinical conditions

1) Testing of all ball/liner combinations prior to clinical study.
2) Wear study at the alumina taper interface (in vitro fatigue to 10 million cycles in saline with a load of 3K Newtons).
3) Testing of all sizes.
4) Range of Motion evaluation for all combinations of liners/stem/head sizes.

B. Clinical protocol conditions

1) Multiple Stems: Encouraged but not required to reduce number of stems.
2) Cemented vs. Cementless stems: Randomization to ceramic vs. non-ceramic group after selection of cemented vs. cementless stem
3) Acetabular Screw: No concern regarding numbers of screws, but numbers of screws used should be recorded, data can be pooled.
4) Cemented Cups: If cemented cups are used, patient should undergo intent to treat analysis i.e. followed over time, and not treated as a study failure.
5) Different Size of Heads Used: Endorsement of statistician's feeling that size of study group should accommodate 28 mm vs. 32 head size analysis.
6) Exclusions to be added: Hip revision and hip fracture
   Exclusions to be removed: osteoporosis
   Inclusions: Bilateral
7) Case report form additions: Recommended except for blood loss.
8) Time Frame: A minimum two year follow-up (can be up to 26 months) should be performed. Yearly follow-up with three month windows should be carried out until the last patient of the study reaches two year follow-up.
9) Guidelines for Acetabular Cup Failure: Two zones with greater than 2 mm or greater of radiolucency.
   Femoral failure: Three contiguous zones with 2 mm or greater of radiolucency. Weight bearing films should be utilized for all analysis.
10) Implant Success: Should be defined as absence of loosening, absence of need for revision.
    Implant Failure: Need SF-36 or WOMAC tests in addition to total HHS (<70) score in addition to two other test criteria mentioned in the PDP.
11) Data Analysis plan taking into consideration longitudinal analysis, bilateral site interaction effects, interaction of other covariates on treatment effects.
12) Delta values set at one-third of standard deviations for continuous measurements or at 5% for proportional.

Based on input from the Panel, the PDP was amended, and approved on July 21, 1998.

XII. FDA Decision

Based on the data provided in the Notice of Completion, the sponsor has adequately met all acceptance criteria as previously agreed to in the approved PDP. Meeting these acceptance criteria demonstrates that the safety and effectiveness of the Encore Keramos™ Ceramic/Ceramic Total Hip System has been sufficiently established, when used as indicated, for FDA to find in favor of approval of this Notice of Completion for this device system.

In addition, a post-approval study that extends the original 24 month study out to 60 months on those patients implanted at three of the study sites will be conducted. Collection of full clinical and radiographic data from all patients implanted at these three sites will provide data on 77 investigational and 78 control cases. Safety and effectiveness data will be collected as specified in the PDP protocol, and reported annually until all patients have reached their 5 year post-operative evaluation. Also, all patients enrolled in the original study cohort (i.e., from *all* 17 sites) will be sent a postcard annually for ten years post-operatively, to assess the patient's general well-being and if the study components are still in place. The postcard will specifically ask the following three questions:

1. Has your hip prosthesis been revised or replaced? (Yes or No)
2. Are you satisfied with how your hip prosthesis is functioning? (Yes or No)
3. Do you expect to have your hip prosthesis removed in the near future? (Yes or No)

A device with a completed PDP is considered to have an approved premarket approval application (PMA) in accordance with section 515(f)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and is subject to the requirements described under 21 CFR 814.

The sponsor's manufacturing facilities were inspected and determined to be in compliance with the Quality System Regulation (21 CFR Part 820).

FDA issued an approval order to the sponsor on November 26, 2003.

XIII. Approval Specifications

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.